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(54) Title: COMPOSITIONS FOR USE IN SURGERY

(57) Abstract: A method is provided for treating a subject in need of medication as an adjunct to elective surgery, comprising administration of a ketogenic material sufficient to produce a physiologically acceptable ketosis in the patient. Preferably the surgery is selected from the groups consisting of removal or section of tumours, removal of redundant organs such as lymph nodes and appendix, open heart surgery, cosmetic surgery, joint and bone surgery.

COMPOSITIONS FOR USE IN SURGERY

The present invention relates to compounds and compositions that have the effect of modulating mammalian central nervous system activity such as to have beneficial effect in surgical procedures where it is desirable to stabilise the patient.

It is well known that surgical procedures are stressful to patients of all age groups, but especially the young and the elderly (eg see Burkhardt et al, 1997; Ornaque et al, 2000; Pace et al, 2004) and premedication prior to surgery is generally employed to reduce the incidence of anxiety, muscle tenseness and insomnia in such patients (eg see Tolksdorf et al, 1987; Drautz et al, 1991; Ornaque et al, 2000; Frank et al, 2002). Drugs employed as premedicating agents include the benzodiazepines (for their anxiolytic, sedative amnesic and muscle relaxant properties), α_2-adrenoceptor agonists (for their sedative, analgesic, anti-emetic and anaesthetic-sparing effects) and opioid/major tranquiliser combinations therapy (also for their sedative, analgesic, anti-emetic and anaesthetic-sparing effects).

In addition, these agents have therapeutic value in the post-operative situation where they are used predominantly to induce sedation (often in critical care situations) and to reduce post-surgical complications and pain (eg see Martin et al, 2003; Moore et al, 1983; Galasko et al; 1985; Reithmuller-Winzen, 1987; Kulka et al 1996; Oliver et al, 1999; Frank et al, 1999, 2002; Kuchta and Golembiewski et al, 2004). However, polypharmacy can lead to unfavourable drug interactions in these patients, particularly in the geriatric population that can result in serious complications and even death. Thus, there is an opportunity in all types of surgery, ie procedures performed under general or local anaesthesia, for the use of a peri-surgical intervention that will provide "stabilisation" for the patient, ie it will produce sedation, anxiolysis, anaesthetic-sparing and/or analgesia, without the potential liability of drug-drug interactions. In this invention, we have demonstrated that ketogenesis unexpectedly provides such a therapeutic intervention.

It is known that both acute and chronic neurodegenerative states in mammals, eg. man, can be treated by inducing ketosis. Such ketosis can be provided by restriction of diet, eg by starvation or exclusion of carbohydrate, or by administration of ketogenic materials, such as triglycerides, free fatty acids, alcohols (eg butan-1, 3-diol), acetoacetate and (R)-3-hydroxybutyrate and their conjugates with each other

and further moieties, eg. esters and polymers of these. Ketogenic materials thus produce a physiologically acceptable ketosis when administered to a patient.

Further therapeutic indications for the application of ketosis include epilepsy, diabetes, dystrophies and mitochondrial disorders. In the case of epilepsy ketogenic diet has been applied in treatment of intractable seizures with some success for many years, although the mechanism by which the seizure suppression is achieved remains uncertain.

Copending patent applications by KetoCytonyx describe how ketogenic materials may be used to provide treatment for depression, impaired cognitive function, pain, apoptotic conditions, attention deficit disorder, (ADHD) and related CNS disorder symptoms of one or more of impaired learning, impaired problem solving and impaired planning, impulsiveness and aggression

The present inventors have been studying the mode of action of ketogenic materials in CNS injury and particularly have studied whole mammalian brain electrical activity with a view to understanding more completely its overall effect on functioning brain.

Surprisingly, they have now found that completely unanticipated changes in brain electrical activity are induced by ketosis in man such that it is evident that ketosis has a beneficial effect in all types of surgery where it is necessary or desirable to stabilise the patient to allow the other aspects of the procedure to proceed safely. In the context of the present invention, 'stabilise' particularly provides sedation and/or anaesthetic sparing preferably with anxiolysis and/or analgesia.

Analysis of brain field potentials ("Tele-Stereo-EEG") has been proven to be a very sensitive tool for the characterization of drug effects on the central nervous system (Dimpfel et al., 1986). After administration of a centrally active drug, quantitative changes in the brain field potentials can be considered as a characteristic fingerprint of that particular drug. "Fingerprints" of more than 100 compounds have been obtained including 8 established drug categories, e.g. analgesics, antidepressants, neuroleptics, stimulants, tranquilizers, sedatives and narcotics (particularly general anaesthetics). Different dosages of the same drug cause quantitative changes in electrical power.

This methodology can therefore also demonstrate possible dose response relationships. Direct comparison with specific reference drugs, or by discriminant analysis with reference to an extensive fingerprint database, permits the detection of

any possible similarities with established drugs. In general, "fingerprints" show prominent differences for drugs prescribed for different indications and are similar for drugs with similar indication (Dimpfel 2003). Furthermore, the pattern of EEG changes in the rat is a useful tool in predicting possible changes in the EEG power spectrum in humans.

Applying this technique to ketosis, particularly that induced by direct administration of (R)-3-hydroxybutyrate sodium salt, the present inventors have been able to show clear changes in the EEG power spectra in human subjects that are consistent with beneficial clinical effects, ie the provision of sedation, anxiolysis and/or analgesia. These are whole brain effects consistent with beneficial effects suited to application to patients undergoing all types of surgery, particularly major surgery.

The present inventors have now studied the effect of ketosis, in the exemplified case induced by administration of sodium salt of (R)-3-hydroxybutyrate (herein referred to as KTX 0101) as a single intravenous infusion of increasing dose and duration to 3 groups (Parts A, B and C) with 3 cohorts of 3 subjects each in Part A, and 1 cohort in each of Parts B (n=3) and C (n=8). Parts A and B were a partial crossover design and Part C was a crossover design. For details see protocol.

A 17-electrode EEG was recorded pre-dose and at 6, 12 and 24 h during the infusion and 1 and 24 hours following the end of drug administration. Recordings were performed under two physiological conditions, namely with 5 minutes eyes open and eyes closed, respectively. KTX 0101 was administered intravenously at a dose of 300 mg/kg given over 24 hours to 1 cohort (n=8) in a double blind placebo controlled crossover design (Part C of the study).

Analysis of the recorded data revealed that consistent deviations from pre-drug values were found during and after the infusion which could be attributed to drug application. Whereas delta and theta power (averaged over 15 electrode positions because data collection from 2 electrodes, ie Fz and Pz, was compromised) decreased under placebo conditions (environmental stress due to infusion of an unknown drug) this effect was not observed under active drug conditions. On the contrary increases of electrical power were observed, especially with respect to theta, alpha and beta power. Using a non-parametric statistical test for comparing time dependent changes between placebo and active drug some differences were observed at the recording time of 6, 12 and 24 hours after the beginning of the KTX0101

infusion with respect to theta, alpha1,2 and beta1,2 frequencies. Increased power changes in the delta, theta, alpha1,2 and beta1 frequencies, some highly statistically significant, were also observed 1h and 24h after termination of the KTX 0101 infusion.

Since the electrical power within the theta and beta frequencies increases during the cooling of patients (see Kochs, 1995), these changes may be interpreted as indicative of a cytoprotective action of KTX 0101 in these subjects as hypothermia has powerful cytoprotective actions (Wagner and Zuccarello, 2005; Lasater, 2005; Citerio et al, 2004). Power increases in the beta range of varying degrees have been observed in rats after administration of sedative analgesics, including phenobarbital (barbiturate sedative, analgesic, anxiolytic, muscle-relaxant), diazepam (benzodiazepine sedative, anxiolytic, amnesic, muscle-relaxant), buprenorphine and morphine (opiate, narcotic analgesics) and flupertine (non-opiate analgesic) (see Dimpfel et al, 1986). These drug classes are all used as pre-medications in surgery and as agents to manage post-operative pain as well as other complications (see Tolksdorf et al, 1987; Drautz et al, 1991; Burkardt et al, 1997; Frank et al, 1999, 2002; Ornaque et al 2000). Combined increases in theta, alpha1,2 and beta1,2 power have also been reported to occur in rats after administration of noradrenergic α_2-adrenoceptor agonists, eg metedomidine, guanfacine, clonidine, maxonidine and (-)lofexidine, (see Dimpfel and Schober, 2001). This class of drug has long been employed in the pre-surgical setting for its sedative, analgesic, anti-emetic and anaesthetic-sparing effects and post-surgically to prolong anaesthesia-induced analgesia and to reduce post-operative shivering (see Kulka et al, 1996; Oliver et al, 1999; El-Kerdawy et al 2000; Frank et al, 2002; Akbas et al, 2005). Lastly, combined increases in alpha1,2 and beta1,2 power have been reported to occur in rats after administration of general anaesthetics, eg halothane, desflurane, enflurane and isoflurothane (halogenated gaseous anaesthetics) and propofol (steroidal injectable anaesthetic), (see Dimpfel, 2003). Together, these changes in the EEG power spectra evoked by infusion of KTX 0101, which are present not only during the infusion period, but also for many hours after, indicate that KTX 0101 has the unexpected ability to provide "stabilisation" to patients in the peri-surgical setting by virtue of its sedative, anxiolytic, aneasthetic-sparing and/or analgesic actions. KTX 0101 is not a pharmacological intervention because it produces its beneficial effects by providing a key substrate of physiological, mitochondrial oxidative phosphorylation, and

therefore, it will not give rise to serious side-effects or adverse events that arise from drug-drug interactions that can arise with conventional agents, eg barbiturates, benzodiazepines, opiates or α_2-adrenoceptor agonists (see Kuchta and Goliembiewski, 2004).

Thus in a first aspect of the present invention there is provided a method of treating a subject in need of medication as an adjunct to elective surgery, comprising administration of a ketogenic material sufficient to produce a physiologically acceptable ketosis in the patient. This takes the application of ketosis into the field of elective surgery in absence of pre-existing trauma eg. of head or trunk and in addition into general surgery (both urgent and non-urgent). Further it is envisaged that this surgery surprisingly might include, but is not limited to, removal of tumours, removal of redundant organs such as lymph nodes and appendix, open heart surgery, cosmetic surgery, joint and bone surgery and organ transplantation etc.

Preferably the ketosis is such that ketone bodies in the patients blood as sufficient to elevate electrical power of one or more of the theta, aphal and betal frequencies in the patients EEG as compared to control levels.

The ketosis produced is preferably a state in which levels of one or both of acetoacetate and (R)-3-hydroxybutyrate concentrations in the blood of the subject are raised. Preferably the total concentration of these 'ketone bodies' in the blood is elevated above the normal fed levels to between 0.1 and 30mM, more preferably to between 0.3 and 15mM, still more preferably to between 0.5 and 10mM and most preferably to between 3 and 8mM. For the purpose of maximising levels of such compounds in the CNS it is desirable to saturate the transporter through which (R)-3-hydroxybutyrate crosses the blood brain barrier: this occurring at between 3 and 5mM.

In its broadest interpretation, the ketogenic material may be any of those used in the treatment of refractory epilepsy, However, in order to avoid undesirable consequeces of such diets preferred materials are selected from acetoacetate, (R)-3-hydroxybutyrate, salts, esters and oligomers of these and conjugates of these with other physiologically acceptable moieties, such as carnitine and other amino acids. Other acceptable materials are metabolic precursors of ketones these such as (R)-1, 3-butandiol, triacetin, free fatty acids and triglycerides.

Particular materials are known from the following references as set out in Table 1 below. Doses and formats are as described in the documents identified in the

table. Typically the amount of ketogenic material required can be determined by measuring blood levels directly using a meter such as the Medisense Precision Extra (MedisenseInc, 4A Crosby Drive Bedford, MA 01730); BioScanner 2000 (formerly called the MTM BioScanner 1000) from Polymer Technology Systems Inc. Indianapolis, Indiana. In this manner the amount of ketosis derived from a set dose may be ascertained, and that dose iterated to suit the individual.

Typical dose ranges for example might be in the range 5 to 5000mg/kg body weight, particularly for an (R)-3-hydroxybuytrate containing material such as oligomeric (R)-3-hydroxybuytrate or its esters with, eg, glycerol or (R)-butan-1,3-diol, more preferably 30 to 2000mg/kg body weight, most preferably 50 to 1000mg/kg body weight per day. Regular blood levels are more readily attained by dosing using a parenteral line through a catheter and drip feed or by a single bolus injection through a saline line.

For parenteral injection asolution containing 1 to 5000mg/kg per day is supplied, typically being the ketogenic material, eg. (R)-3-hydroxybutyrate in aqueous solution, such as in water or in saline.Such solution for bolus injection may be from 5 to 500mM, preferably 28 to 300mM, concentration for injection or higher concentration as a cincentrate for dilution in a drip. Where the ketogenic material is not water soluble it may be administered as an injectable emulsion such as will be known to those skilled in the art.

In a second aspect of the present invention there is provided the use of a ketogenic material for the manufacture of a medicament for administration in surgery, whether as premedication or during the course of the surgery. Such surgery is advantageously that which is is either elective or general surgery (both urgent and non-urgent), as opposed to that required for a pre-existing trauma as is already taught is treatable in the prior art.

Again, suitable ketogenic materials are as described for the first aspect of the invention and as exemplified in Table 1.

A third aspect of the present invention provides a pharmaceutical composition for use in surgery, the surgery particularly being that which is either elective or general surgery (both urgent and non-urgent), rather than that associated with head or trunk trauma. Surgery to remove a tumour, section of gut or tissue is thus contemplated.

TABLE 1 Documents incorporated herein by reference

Material	Type	Reference
Sodium (R)-3-hydroxy-butyrate	Salt	US 4579955 US 4771074
(R)-1, 3-butandiol	Metabolic precursor	Gueldry al (1994) Metabolic Brain Disease Vol 9 No2
Acetoacetylbutandiol	Metabolic precursor	US 4997976 US 5126373
Dimer and trimer BHB	Metabolic precursor	JP 5009185 JP 2885261
Acetoacetyltri-3HB	Metabolic precursor	US 6207856
Mid chain triglyceride	Metabolic precursor	WO 01/82928
Triolide	Metabolic precursor	WO 00/15216 WO 00/04895
BHB-triglyceride	Metabolic precursor	US 5420335 US 6306828
BHB multimers	Metabolic precursor	WO 00/14985

The present invention will now be described by way of the following non-limiting Examples and Figures. Further embodiments falling into the scope of the claims herein will occur to those skilled in the light of these.

FIGURES

Figure 1: Documentation of changes at single electrode positions in percent of pre-dose values for each of the recording times: 6, 12 and 24 h during infusion of KTX 0101 (300 mg/kg iv infused over 24h) and 1 h and 24 post-infusion (pi). Bar graphs represent frequency ranges from delta (1st left column), theta (2nd left), alpha1 (3rd left), alpha2 (4th left), beta1 (5th left) and beta2 (right column). Cortical electrode positions are labeled as C for central, F for frontal, T for temporal, P for parietal, O for occipital. Even numbers refer to the right hemisphere, odd numbers to the left hemisphere. Results from the ΦFz and ΦPz electrode positions (crossed-out on the

Figure) were not included because of unreliable outputs from them. Data are shown for the condition: "eyes open".

Figure 2: Documentation of changes at single electrode positions in percent of pre-dose values for each of the recording times: 6, 12 and 24 h during infusion of KTX 0101 (300 mg/kg iv infused over 24h) and 1 h and 24 post-infusion (pi). Bar graphs represent frequency ranges from delta (1st left), theta (2nd left), alpha1 (3rd left), alpha2 (4th left), beta1 (5th left) and beta2 (right). Electrode positions are labeled as C for central, F for frontal, T for temporal, P for parietal, O for occipital. Even numbers refer to the right hemisphere, odd numbers to the left hemisphere. Results from the ΦFz and ΦPz electrode positions (crossed-out on the Figure) were not included because of unreliable outputs from them. Data are shown for the condition: "eyes closed".

Figure 3: Time-course of recording periods during placebo administration. The infusion period for placebo was 24 h. Recordings were taken pre-dose, 6, 12 and 24 h during infusion and 1 and 24 h post-infusion (pi). Recording periods consist of 5 minutes "eyes open" (Eo) followed by 5 minutes "eyes closed" (Ec) for each time-point. Global median of power is shown.

Figure 4: Time-course of recording periods during drug administration. Infusion period was 24 h. Recordings were taken pre-dose, 6h, 12 and 24 h during infusion and 1 and 24 h post-infusion (pi). Recording periods consist of 5 minutes "eyes open" (Eo) followed by 5 minutes "eyes closed" (Ec) for each time-point. Global median of power is shown.

Figure 5: Documentation of electrical power changes at recording periods during and following placebo and KTX 0101 (300 mg/kg iv over 24h) infusion for the condition "eyes open". Pre-dose values were set to 100% (represented by dotted line). The effects of placebo are shown by the light shading in the histobars and those of KTX 0101 (300 mg/kg iv infused over 24h [denoted as Verum]) are shown by the dark shading. Each frequency range is shown separately from delta, through theta, alpha1, alpha2, beta1 and beta2. For definition of frequency ranges see Methods (below).

Figure 6: Documentation of electrical power changes at recording periods during and following placebo and KTX 0101 (300 mg/kg iv over 24h) infusion for the condition "eyes closed". Pre-dose values were set to 100% (represented by dotted line). The effects of placebo are shown by the light shading in the histobars and those of KTX 0101 (300 mg/kg iv infused over 24h [denoted as Verum]) are shown by the dark shading. Each frequency range is shown separately from delta, through theta, alpha1, alpha2, beta1 and beta2. For definition of frequency ranges see see Methods (below).

METHODS.

Since functional changes of brain activity can most easily be accessed by recording electrical activity from the scalp, advanced EEG technology (CATEEM®) was used to characterize the effects of KTX 0101 on the brain.

Monitoring brain activity by quantitative EEG

Monitoring the electrical activity of the human brain has been a major challenge since the first report on the feasibility of its measurement by the German researcher Hans Berger in 1929 (Berger 1929). As early as 1932, he together with Dietsch suggested to use the mathematical approach of frequency analysis in order to quantitatively describe the information content of the recorded signals (Dietsch and Berger 1932). This idea had to await modern computer technologies available since the 1960's (Fink *et al* 1967) to perform the necessary calculations within a reasonable time. Since then an ever-increasing amount of literature describes changes of electrical activity of the brain in response to disease states, drug administration and behavioral states (Saletu and Grünberger 1988, Itil *et al* 1991, Itil and Itil 1995). Reflection of mental work on the topographical EEG was proven following this (Schober *et al* 1995).

Study design

The study was designed to meet a number of objectives. The main objectives was to obtain safety and pharmacokinetic data which are reported separately. The other objective was to gain preliminary information on possible changes of electrical

activity of the human brain since this activity is a very sensitive marker of possible actions of the drug on the brain.

Single rising doses of KTX 0101 or placebo were administered to groups of healthy male volunteers according to a pre-specified dose escalation schedule (see main report). Incremental doses were administered in a stepwise manner proceeding to each higher dose only if the drug was well tolerated and the criteria for stopping dosing had not been met. The last two cohorts obtained the highest doses of 300 mg/kg and consisted of enough volunteers to justify a preliminary evaluation of recorded EEG data in order to obtain information on the pharmacodynamic effects of the potential drug. After recording of pre dose values the infusion was started and continued for 24 hours. EEG recordings took place during the infusion (6, 12 and 24 h) and 1 and 24 h after the end of the infusion. Each recording period was performed under 5 minutes eyes open and 5 minutes of eyes closed condition.

METHODOLOGY

EEG-analysis

The EEG was recorded bipolarly from 17 surface electrodes according to the international 10/20 system with Cz as a physical reference electrode (Computer aided topographical electro-encephalo-metry: CATEEM® from MediSyst GmbH, 35440 Linden, Germany), using an electrocap. The raw signals were amplified, digitized (2048 Hz/12 bit) and transmitted via fiber optical devices to the computer. The automatic artefact rejection of the CATEEM®-System, which eradicates EEG-alterations caused by eyeblinks, swallows, respiration, ect. during the recording was automatically controlled and individually adjusted by the investigator. ECG and EOG were recorded in one channel each in order to facilitate detection of those signals superposing on to the EEG. The artefact rejection set-up was observed for about 5 minutes prior to the start of the recording to ensure, that all artefacts were correctly eliminated from further evaluation. For safety purposes the original raw data was saved on optical disk in order to allow re-evaluation of the artefact rejection mode if necessary. In these cases the experimental session was re-examined offline with a newly adapted rejection mode. The amount of rejected data was determined automatically and given in percent of total recording time. Nevertheless the entire recording and the computer-based automatic artefact rejection were continuously

supervised and adjusted by a trained technician (Schober and Dimpfel, 1992). The data was recorded under two physiological conditions over a period of 5 minutes each (eyes open and eyes closed).

Using a Lagrange interpolation, signals from 82 additional virtual electrodes were calculated to provide high resolution topographical maps. The signals of all 99 electrode positions (17 real and 82 virtual) underwent the Fast Fourier Transformation (FFT) based on 4-second sweeps of data epochs (Hanning window). Data were analysed from 0.86 to 35 Hz using the CATEEM® software. In this software the resulting frequency spectra are divided into six frequency bands: delta (1.25 - 4.50 Hz), theta (4.75 - 6.75 Hz), alpha1 (7.00 - 9.50 Hz), alpha2 (9.75 - 12.50 Hz), beta1 (12.75 - 18.50 Hz) and beta2 (18.75 - 35.00 Hz). This frequency analysis is based on absolut spectral power values. Data acquisition and analysis were carried out simultanously and provided topographical maps displayed on-line on the computer screen. The resultant recordings from each time point were concatenated to form a single file for each administration (i.e. each study day) in order to present a continuous time course of drug effect. Data of the time course are presented as median over all 17 electrode positions (global median).

3.2 Raw data documentation and statistical analysis

Following a check of the raw data for optimal artifact rejection (new offline analysis was performed), the data was concatenated to give a single file for each subject containing all recording periods for eyes open and closed conditions. Subsequently, group files were built for each recording period and recording condition for documentation and statistical analysis.

Results are presented for each electrode position, as a time course of global median power and bar graphs showing the difference between placebo and active drug for each recording period. In order to analyse any changes induced by KTX 0101, the data from the pre-dose period was set to 100% and changes were calculated and depicted in relation to these values for the condition eyes open and closed separately. Values obtained for each recording period were averaged to give median values. The quartiles have not been depicted since statistical testing was performed for each recording period and frequency.

For statistical evaluation the non-parametric Wilcoxon-Whitney test was used though a partial cross-over design was used. This can be justified since only an

explorative statistic evaluation was intended. At least 5 elements per group were evaluated using this statistical methodology (some subjects did not have a suitable recording). Data were successfully analysed for n=5-6 subjects. As it was a preliminary study in a small number of volunteers, the following statistical differences were considered to be of biological significance, viz $P \leq 0.20$, $P \leq 0.10$, $P \leq 0.05$ (80%, 90% and 95% probabilities, respectively, of a difference between placebo and drug effect)

RESULTS

Effect of intravenous 300 mg /kg on the electrical brain activity during eyes open.

Quantitative evaluation of EEG data was done by recording the electrical activity of the pre-dose phase for 5 minutes during the physiological condition eyes open and closed, respectively. Subsequent recording periods (5 min eyes open and 5 min eyes closed) were performed at 6, 12 and 24 hours during intravenous administration of KTX 0101 (300 mg/kg iv infused over a 24h period) and 1h and 24 h thereafter.

As documented in Fig. 1 the placebo infusion resulted in decreases of slow wave delta and theta power accompanied by some increases in fast frontal and temporal beta power. Under the condition of active drug an increase of delta and theta power as well as of alpha power is observed. These changes are most pronounced at 6 hours during the infusion, decreasing somewhat at the 12 h value but continued to be rather obvious during the rest of the recording time. Unfortunately there were some artefacts on the electrode positions Fz and Pz during the pre-dose time. Therefore these positions have been excluded from further quantitative analysis. Especially with respect to the parietal P3 and P4 electrodes we see firstly clear increases of delta and theta power at 6 h during infusion, then increases in alpha2 power at 12 h and finally alpha1 increases in addition at the end of infusion at 24 h. These effects decrease somewhat at 1 h after the end of infusion but are still observed extensively at 24 h after the end of infusion. Fig. 3 shows the time course of the changes for the median of 15 electrode positions (Fz and Pz were omitted because of artefacts during the pre-dose recording) for the placebo and active drug conditions, respectively. Averages of electrical power for each recording period in relation to pre-dose values are given in Fig. 5. As can be seen from the graphs the difference between placebo and active

drug is largest for the theta, alpha1 and alpha2 power during the infusion period. There are still remarkable differences up to 24 h after end of the infusion.

Effect of intravenous 300 mg/kg on the brain activity during eyes closed

Quite similar changes were seen under the condition of eyes closed. There was some decrease of slow waves, especially during the later hours, but in general the recordings showed stabile conditions. In the presence of active drug, increases of electrical power could be observed for the 6 h time period, less for the 12 h period but consistently thereafter. These increases were seen mostly in the centro-parietal regions of the brain and were confined to theta, alpha1, alpha2 and beta 1 frequency ranges. A detailed statistical analysis is given in Table 1. Fig. 4 shows the time course of the changes for the median of 15 electrode positions (Fz and Pz were omitted because of artefacts during the pre-dose recording). Averages of electrical power for each recording period are given in Fig. 6. Essentially identical differences between placebo and active drug were seen under this condition of eyes closed. Statistical evaluation showed that the changes observed were highly significant at 6 h during the infusion but also with regard to the post-infusion period of 24 h. Details are given in Table 1.

Table 1 Statistical analysis (Wilcoxon-Whitney) comparing placebo with active drug at the different recording periods with respect to single frequency ranges. Numbers represent p-values of significances.

Eyes Closed

Time	Delta	Theta	Alpha1	Alpha2	Beta1	Beta2
6h pt		0,10			0,07	0,07
12h pt						
24h pt	0,07					
1h pt	0,14		0,14	0,14	0,06	
24h pt	0,14	0,14	0,14			

Eyes Open

Time	Delta	Theta	Alpha1	Alpha2	Beta1	Beta2
6h pt		0,07	0,07			
12h pt			0,14		0,14	
24h pt						
1h pt					0,09	
24h pt	0,14	0,14	0,02	0,03	0,09	

ohne Pz+Fz

Thus differences between placebo and KTX 0101 could be observed mainly with respect to middle frequencies (theta, alpha and beta1). Increases of the electrical power were seen in relation to pre-dose values only in the active drug cohort. The changes lasted longer than the duration of the infusion and could be traced up to 24 hours thereafter.

5. DISCUSSION

Since the electrical power within the theta and beta frequencies increases during the cooling of patients (see Kochs, 1995), these changes may be interpreted as indicative of a cytoprotective action of KTX 0101 in these subjects and this finding is entirely consistent with the known actions of the compound (see Smith et al, 2005). What was unexpected was to discover that KTX 0101 infusion evoked changes in the EEG power spectrum similar to those of drugs including barbiturates, opiates, benzodiazepines, and α_2-adrenoceptor agonists, which are in used both as premedications in surgical procedures and as agents to manage post-operative pain and stress as well as other complications. Thus, power increases in the beta range of varying degrees have been observed in rats after administration of sedative analgesics, including phenobarbital (barbiturate sedative, analgesic, anxiolytic, muscle-relaxant), diazepam (benzodiazepine sedative, anxiolytic, amnesic, muscle-relaxant), buprenorphine and morphine (opiate, narcotic analgesics) and flupertine (non-opiate analgesic) (see Dimpfel et al, 1986). These drug classes are all used as pre-medications in surgery and as agents to manage post-operative pain as well as other complications (see Tolksdorf et al, 1987; Drautz et al, 1991; Burkardt et al, 1997; Frank et al, 1999, 2002; Ornaque et al 2000). Combined increases in theta, alpha1,2 and beta1,2 power have been reported to occur in rats after administration of noradrenergic α_2-adrenoceptor agonists, eg metedomidine, guanfacine, clonidine, maxonidine and (-)lofexidine, (see Dimpfel and Schober, 2001). This class of drug has long been employed in the pre-surgical setting for its sedative, analgesic, anti-emetic and anaesthetic-sparing effects and post-surgically to prolong anaesthesia-induced analgesia and to reduce post-operative shivering (see Kulka et al, 1996; Oliver et al, 1999; El-Kerdawy et al 2000; Frank et al, 2002; Akbas et al, 2005). Lastly, combined increases in alpha1,2 and beta1,2 power have been reported to occur in rats after administration of general anaesthetics, eg halothane, desflurane, enflurane and isoflurothane (halogenated gaseous anaesthetics) and propofol (steroidal injectable anaesthetic), (see Dimpfel, 2003). When comparing the EEG effects induced by KTX 0101 to those of the drugs described above, the most marked similarity exists between its actions and those previously reported for the non-opiate analgesic, flupertine (Dimpfel et al, 1986), with strong similarities also to those of the α_2-adrenoceptor agonists, moxonidine and (-)lofexidine (Dimpfel and Schober, 2001) and the general anaesthetics, propofol and enflurane (Dimpfel, 2003).

Together, these changes in the EEG power spectra evoked by infusion of KTX 0101, which are present not only during the infusion period, but also for many hours thereafter, indicate that KTX 0101 has the unexpected ability to provide "stabilisation" to patients in the peri-surgical setting by virtue of its sedative, anxiolytic, anaesthetic-sparing and/or analgesic actions. KTX 0101 is not a pharmacological intervention because it produces its beneficial effects by providing a key substrate of physiological, mitochondrial oxidative phosphorylation, and therefore, it will not give rise to serious side-effects or adverse events that arise from drug-drug interactions that can arise with conventional agents, eg barbiturates, benzodiazepines, opiates or α_2-adrenoceptor agonists (see Kuchta and Goliembiewski, 2004).

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CLAIMS.

1. A method of treating a subject in need of stabilisation as an adjunct to surgery comprising administration of a ketogenic material sufficient to produce a physiologically acceptable ketosis in the patient.

2. A method of treating a subject in need of medication as perisurgical adjunct to surgery, comprising administration of a ketogenic material sufficient to produce a physiologically acceptable ketosis in the patient.

3 A method as claimed in Claim 1 wherein the treatment is performed under general or local anaesthesia.

4 A method as claimed in Claim 1 wherein the treatment is for sedation and/or anaesthetic-sparing.

5 A method as claimed in Claim 2 wherein the treatment provides anxiolysis and/or analgesia.

6 A method as claimed in any one of the preceding claims wherein the surgery is selected from the group consisting of removal or section of tumours, removal of redundant organs such as lymph nodes and appendix, cardio-thoracic, gynaecological, urological, opthalmological, cosmetic and orthopaedic surgery, neurosurgery and organ transplantation.

7. A method as claimed in any one of the preceding claims wherein the surgery is selected from the group consisting of open heart surgery and joint and bone surgery.

8. A method as claimed in Claim 1 wherein the ketosis produced is such that the total concentration of acetoacetate and (R)-3-hydroxybutyrate in the blood of the subject is raised to between 0.1 and 30mM.

9. A method as claimed in Claim 1 wherein the total concentration of acetoacetate and (R)-3-hydroxybutyrate in the blood is between 0.5 and 15mM.

10. A method as claimed in Claim 1 wherein the total concentration of acetoacetate and (R)-3-hydroxybutyrate in the blood is raised to between 1 and 10mM.

11. A method as claimed in Claim 1 wherein the total concentration of acetoacetate and (R)-3-hydroxybutyrate in the blood is raised to between 3 and 8mM.

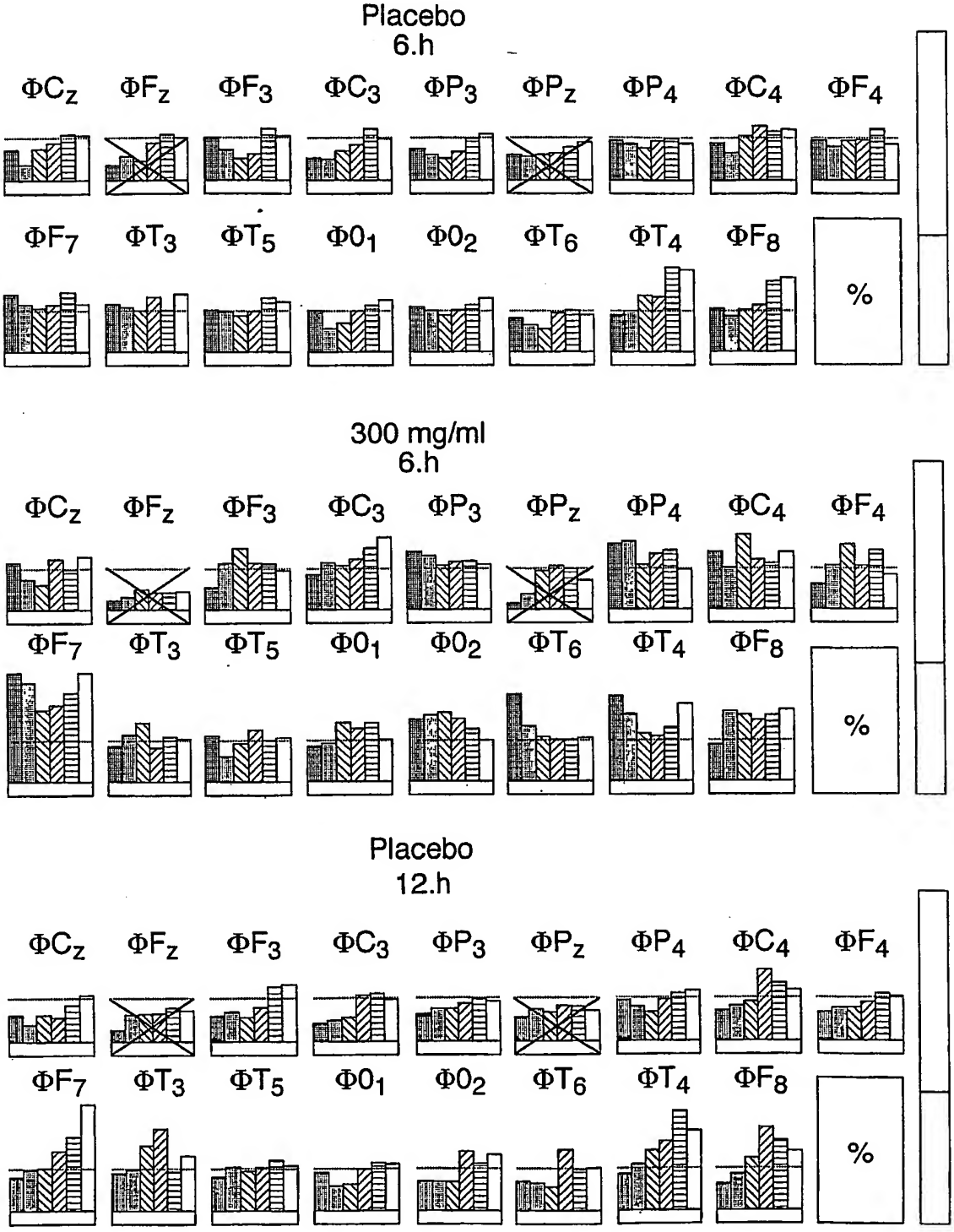
12. Use of a ketogenic material for the manufacture of a medicament for stabilising a patient during surgery.

13. A pharmaceutical composition for use to stabilise a patient for surgery comprising an injectable solution or emulsion of a ketogenic material.

14. A composition as claimed in Claim 9 being in sterile and pyrogen free form.

15. A method, use or composition as claimed in any one of Claims 1 to 9 characterised in that the ketogenic material is selected from the group consisting of triglycerides, free fatty acids, alcohols (eg butan-1,3-diol), acetoacetate and (R)-3-hydroxybutyrate and their conjugates with each other and further moieties, eg. esters and polymers of these.

Fig.1.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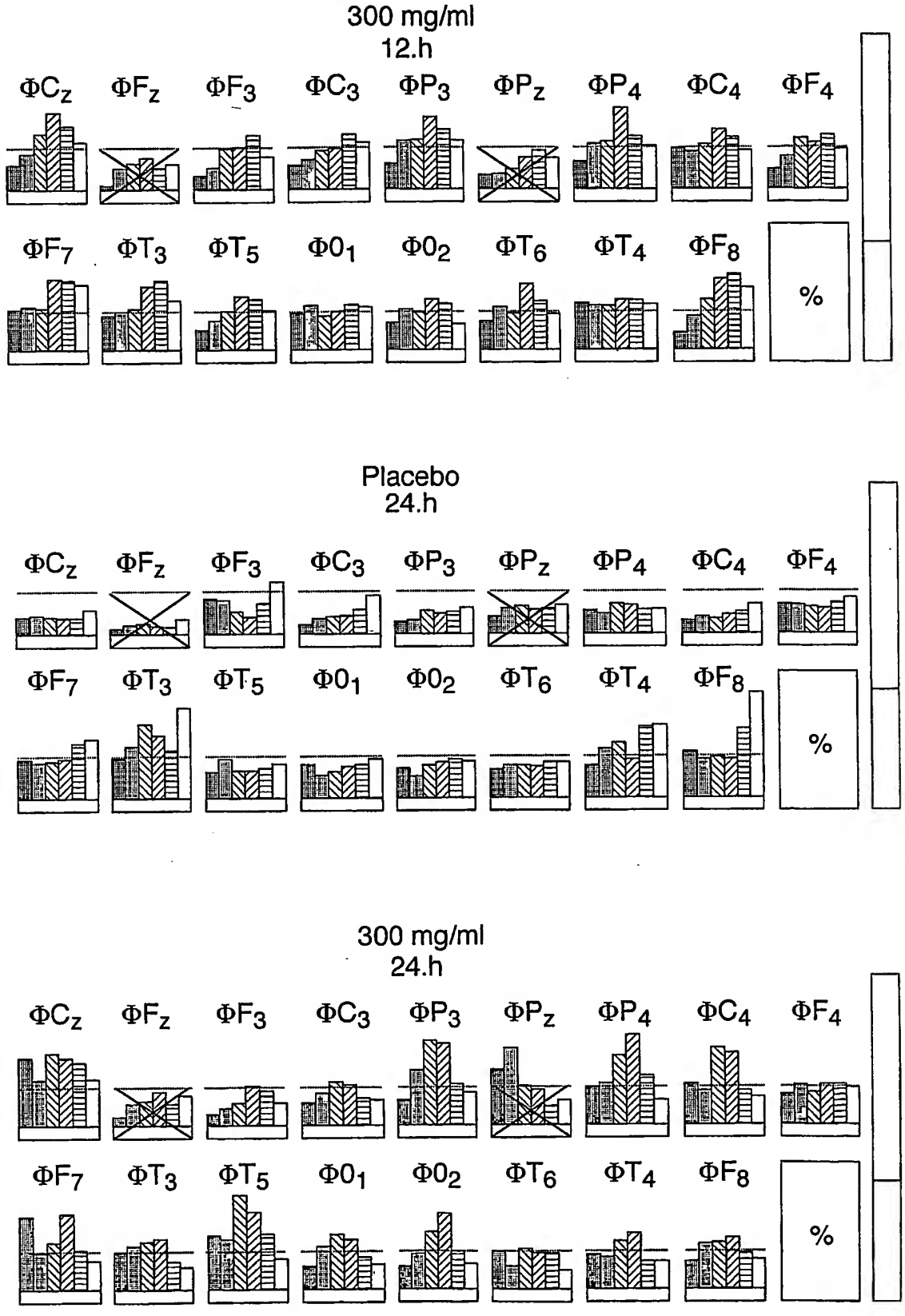
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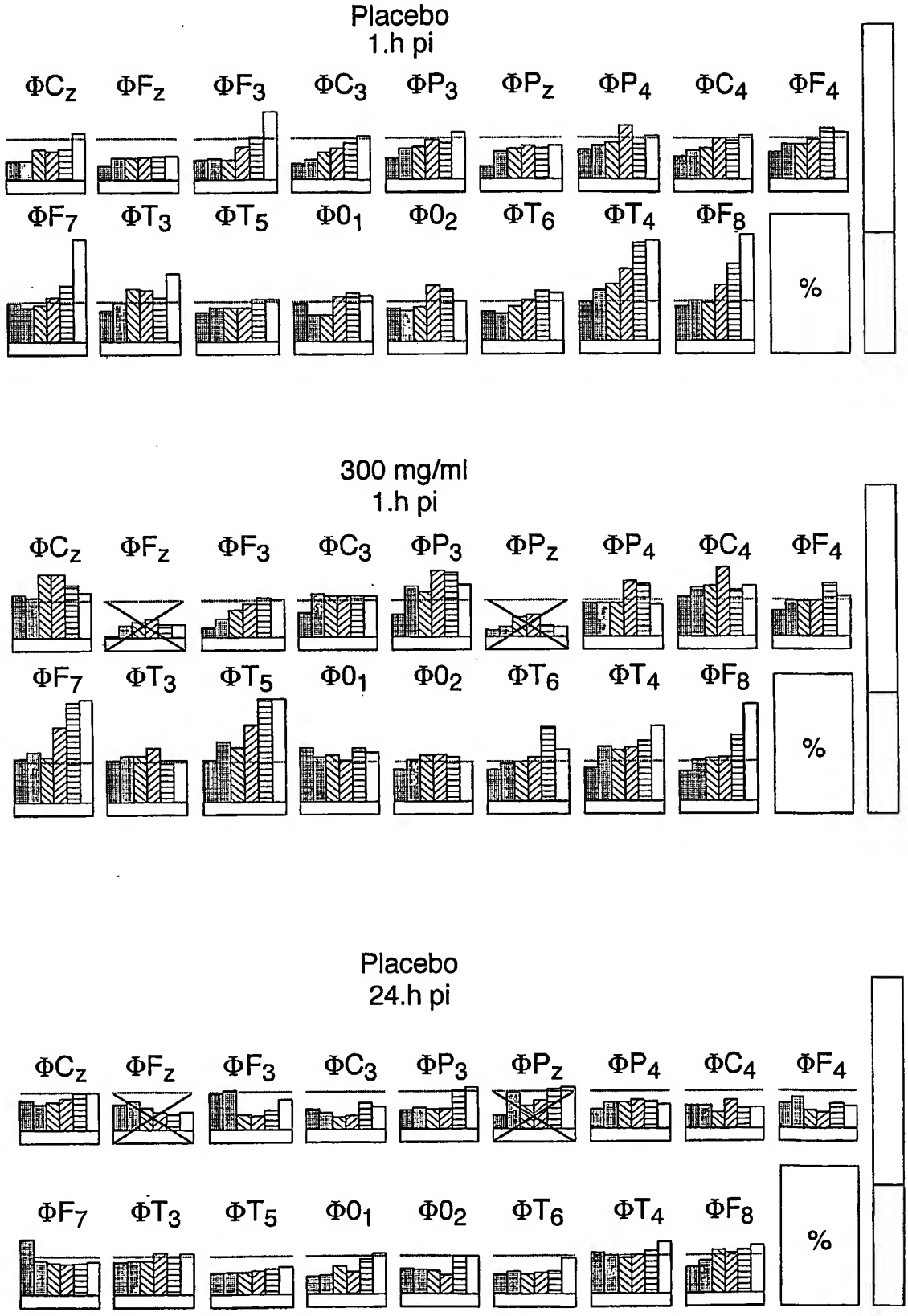
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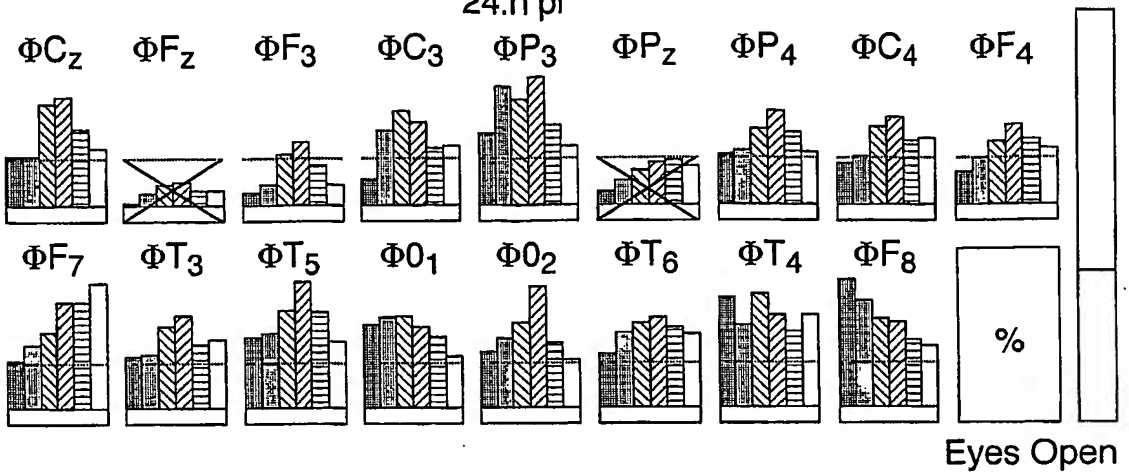

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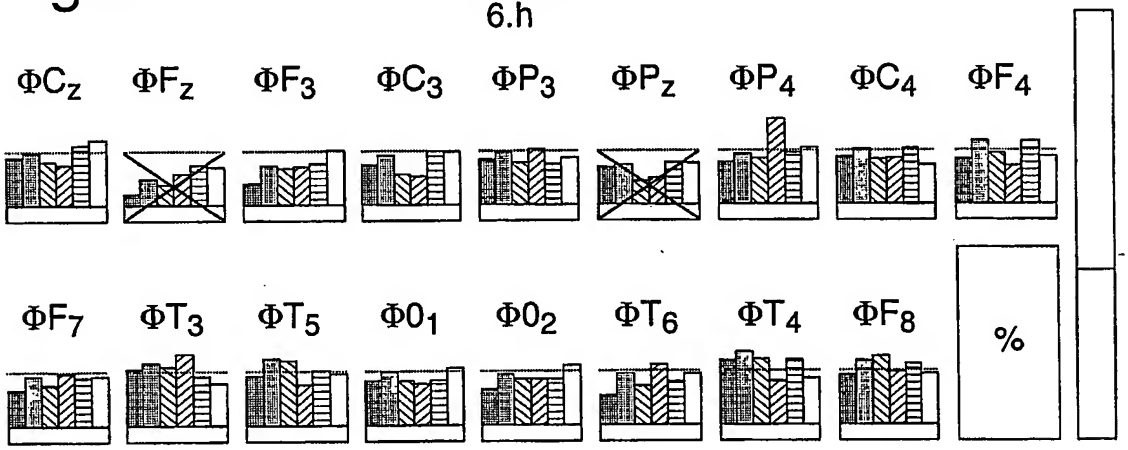

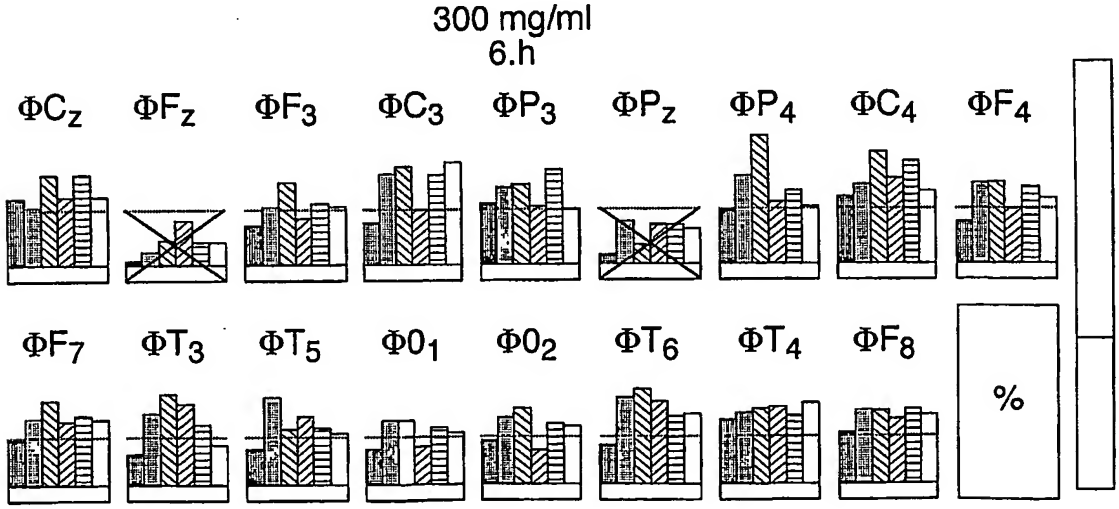

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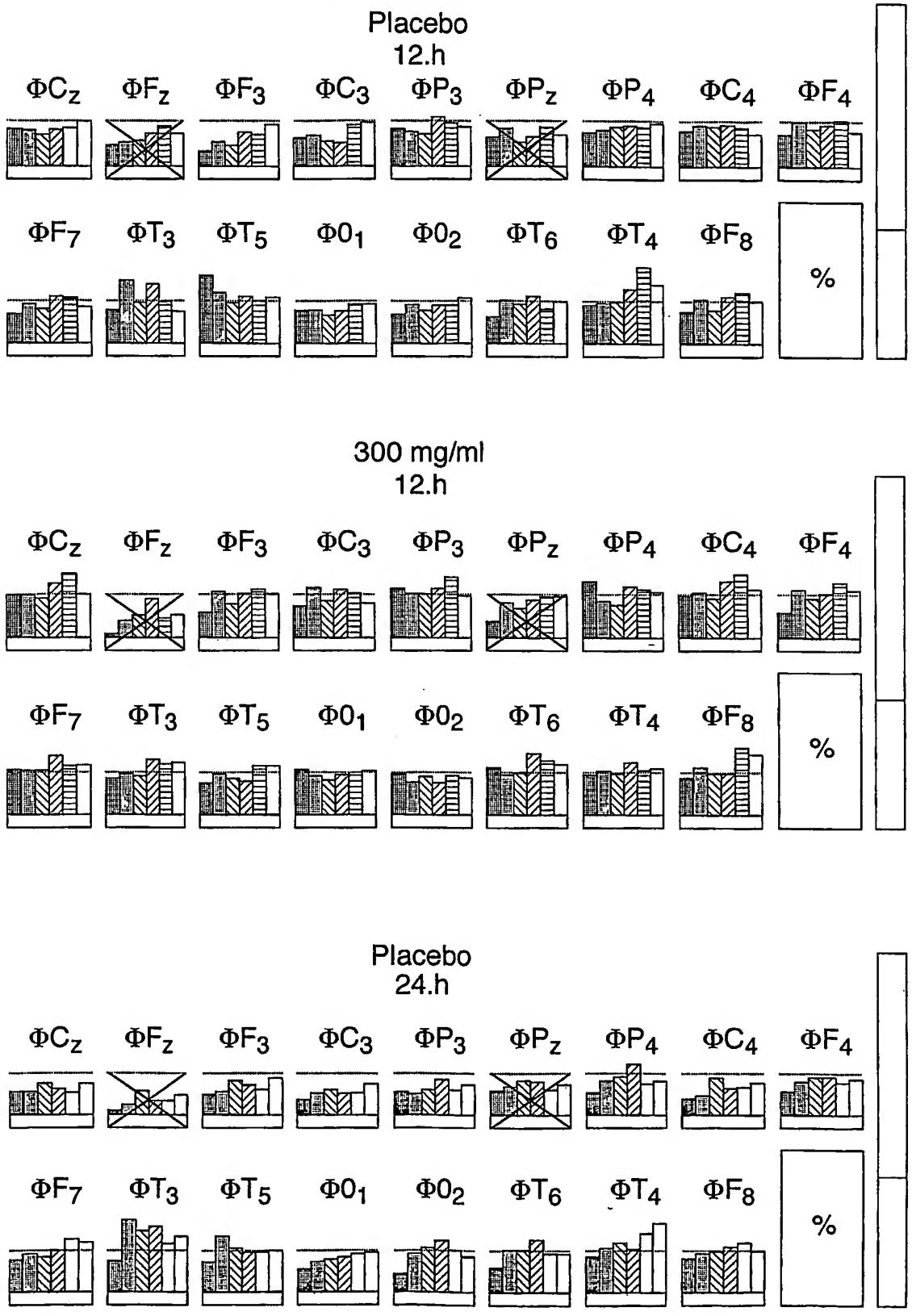
Fig.2 (cont I)



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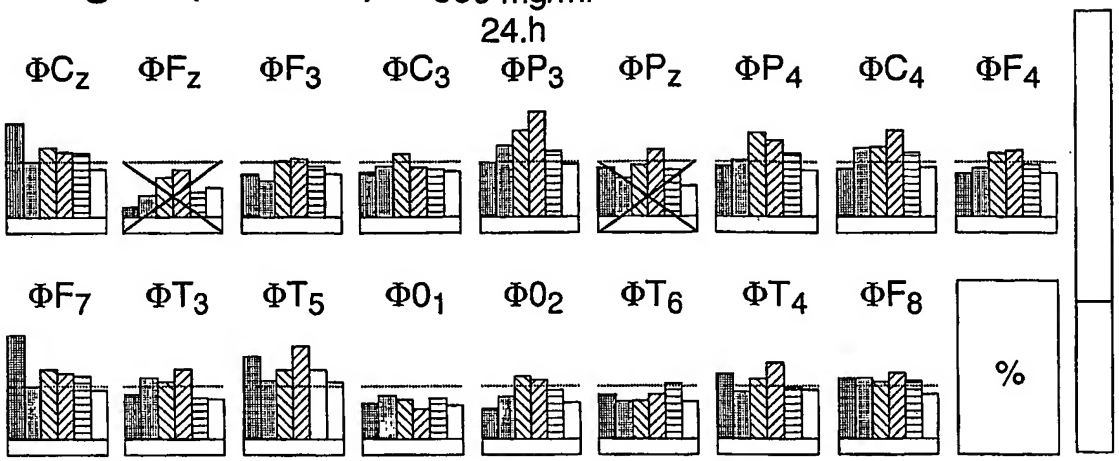
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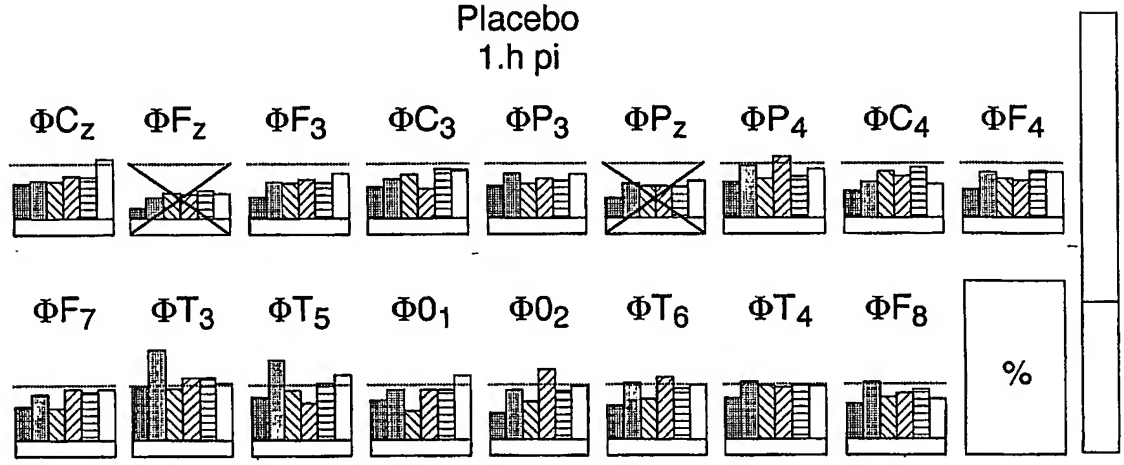
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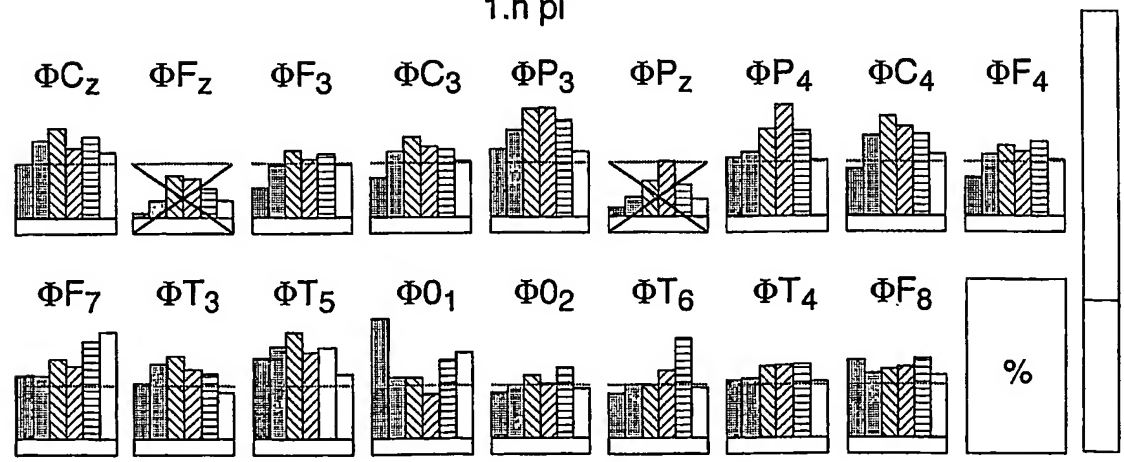
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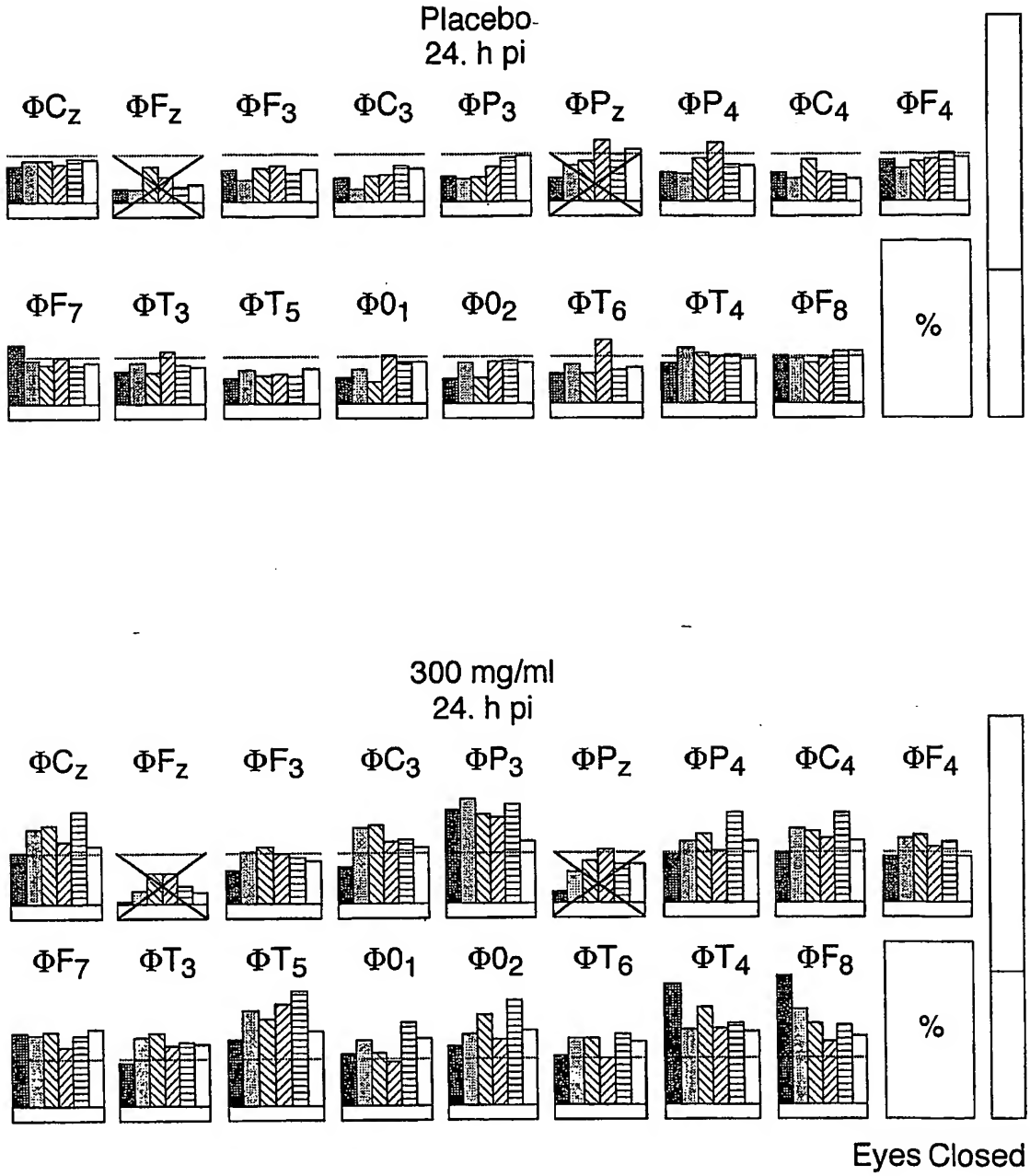
Fig.2 (cont III).



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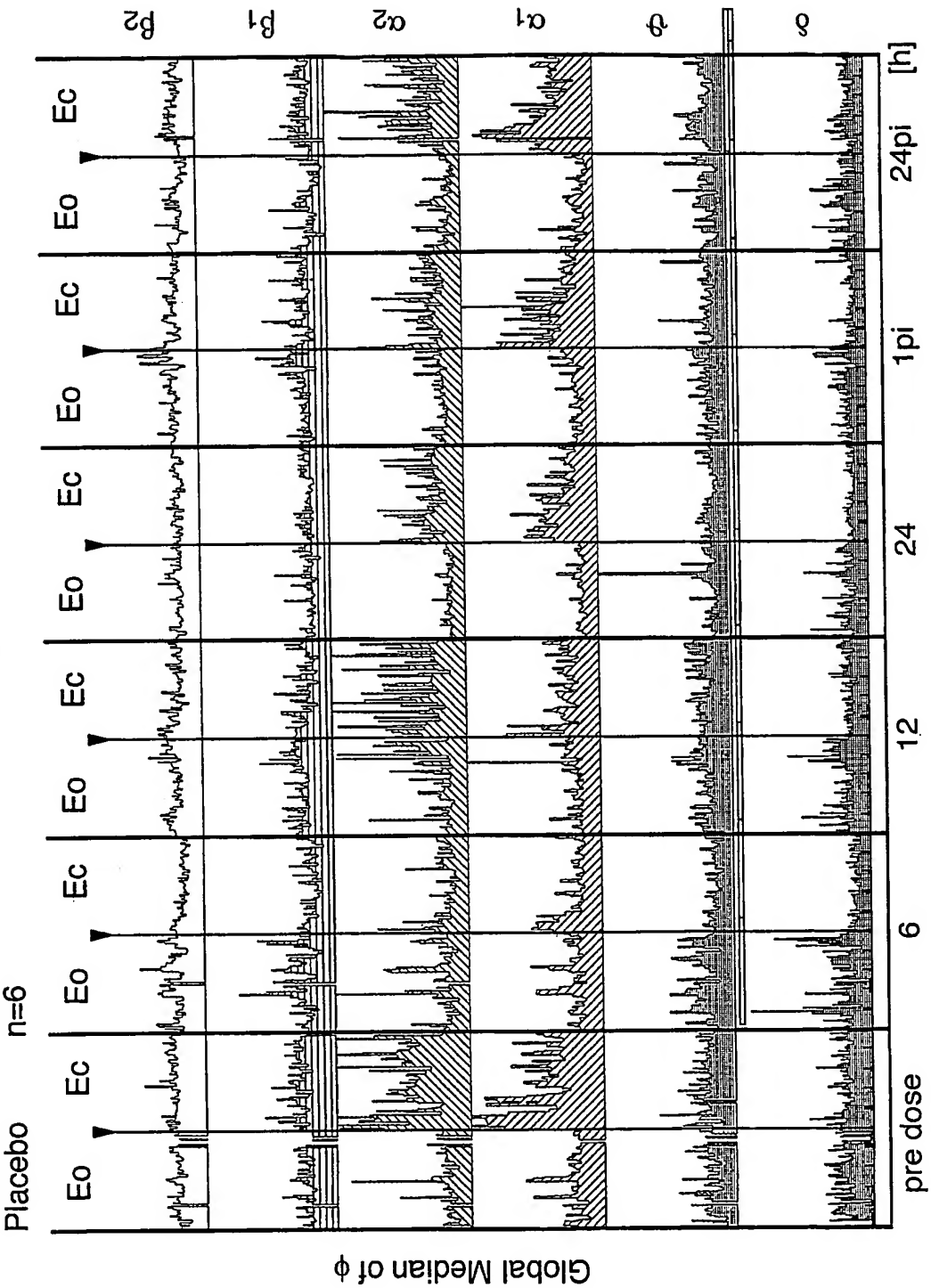
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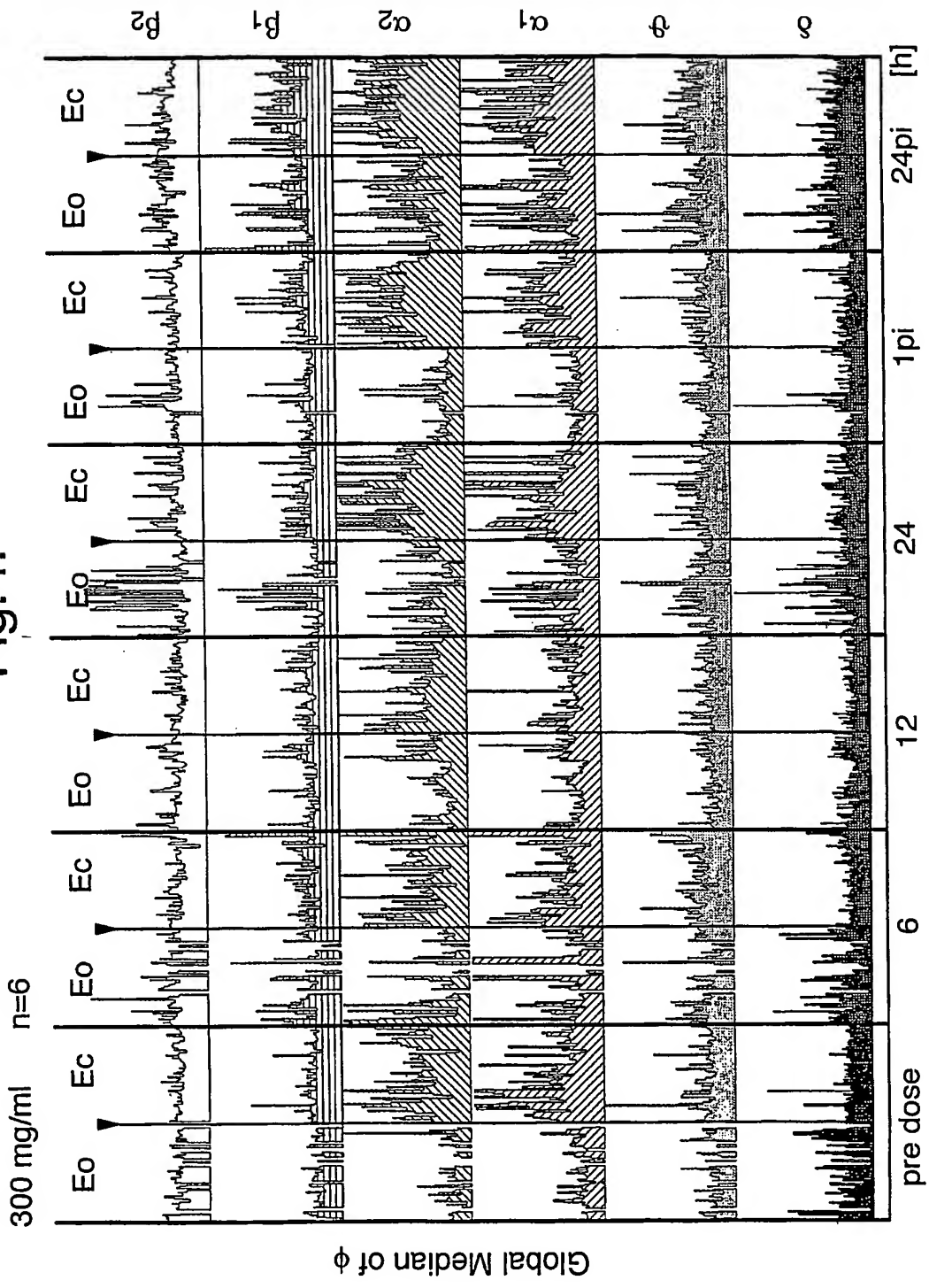
Global Median of ϕ

Fig.4.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Global Median of ϕ

Fig.5.

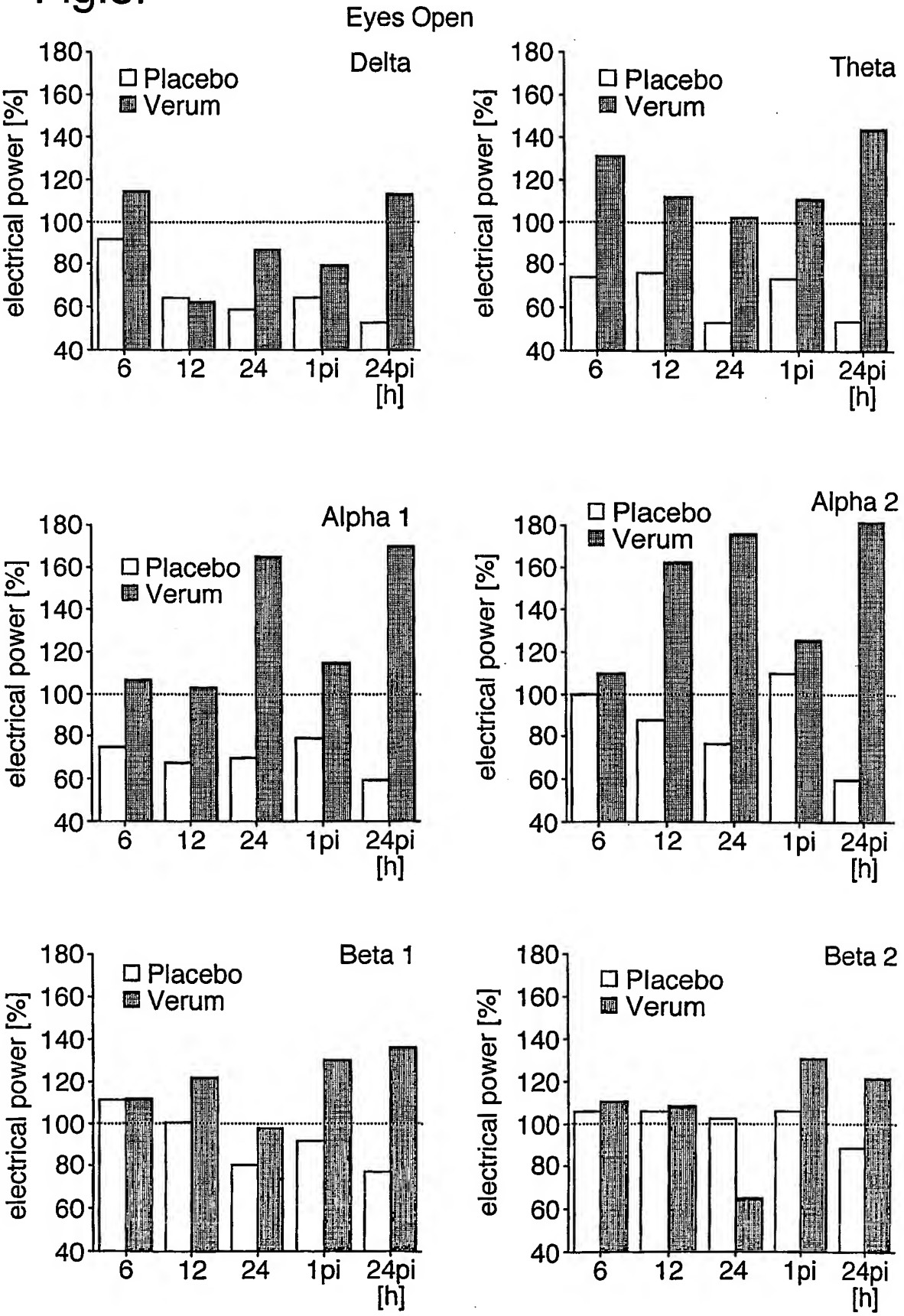
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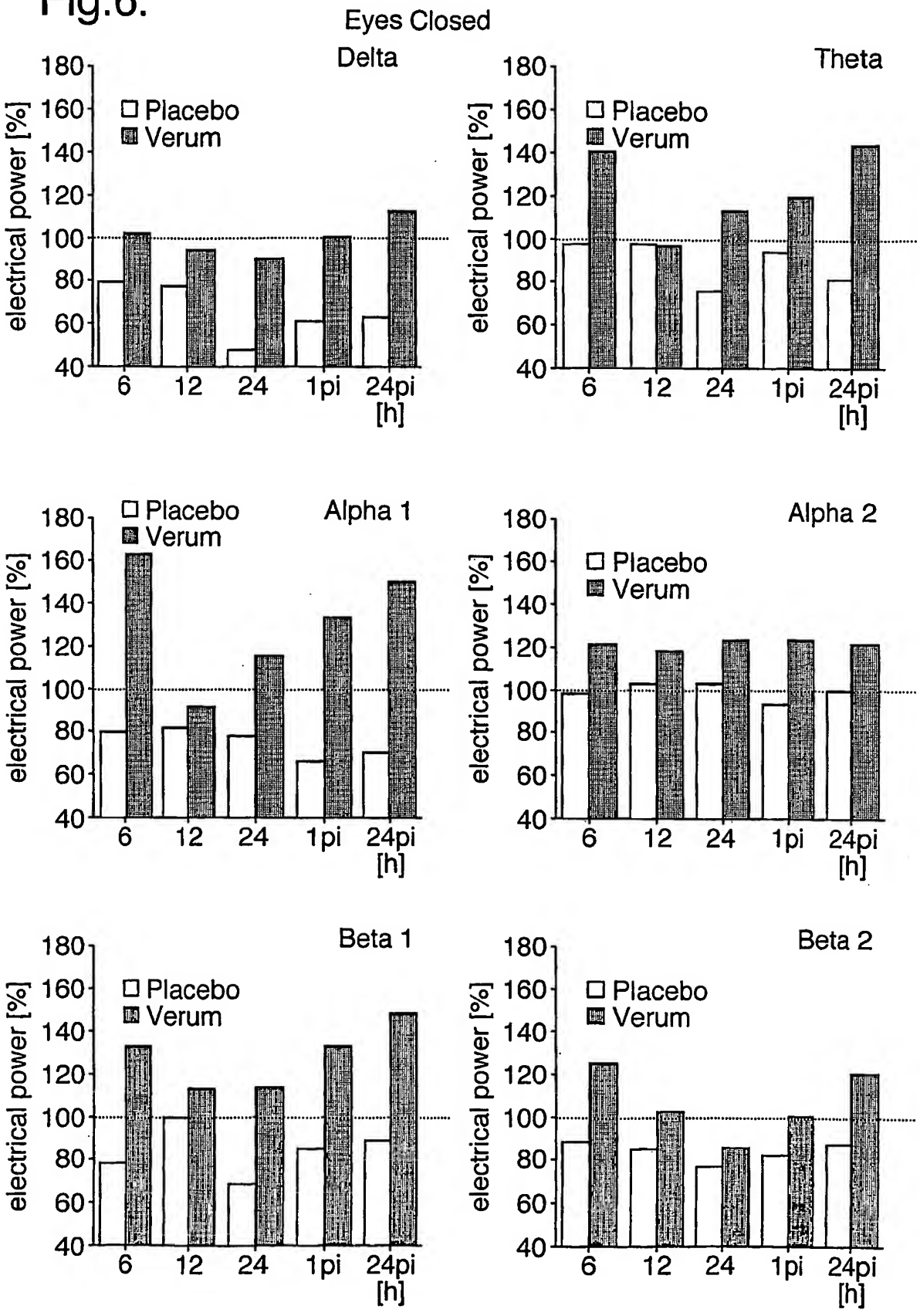
Fig.6.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INTERNATIONAL SEARCH REPORT

International application No
/GB2005/004723

A. CLASSIFICATION OF SUBJECT MATTER
A61K31/19 A61P25/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, EMBASE, WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 2005/107875 A (KETOCYTONYX INC; GREENWOOD, DAVID; DIMPFEL, WILFRIED) 17 November 2005 (2005-11-17) the whole document	1-15
P,X	SMITH S L ET AL: "KTX 0101: A potential metabolic approach to cytoprotection in major surgery and neurological disorders" CNS DRUG REVIEWS 2005 UNITED STATES, vol. 11, no. 2, 2005, pages 113-140, XP009061052 ISSN: 1080-563X abstract	1-15
A	US 5 654 266 A (CHEN ET AL) 5 August 1997 (1997-08-05) column 6	1-15

-/--

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
7 February 2006	15/02/2006
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer Collura, A

Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	MANKES R F ET AL: "Birthweight depression in male rats contiguous to male siblings in utero exposed to high doses of 1,3-butanediol during organogenesis" JOURNAL OF THE AMERICAN COLLEGE OF TOXICOLOGY 1986 UNITED STATES, vol. 5, no. 4, 1986, pages 189-196, XP009061055 abstract	1-15
A	US 2002/013339 A1 (MARTIN DAVID P ET AL) 31 January 2002 (2002-01-31) abstract	1-15
A	WO 01/19361 A (TEPHA, INC; METABOLIX, INC) 22 March 2001 (2001-03-22) page 10, last paragraph - page 11, paragraph 1	1-15

INTERNATIONAL SEARCH REPORT

ternational application No.
PCT/GB2005/004723

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 1-11,15 (with respect to IA)
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 1-11 and 15 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
/GB2005/004723

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2005107875 A	17-11-2005	NONE	
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